

INTRAVENOUS ARTESUNATE: THE NEW GENERATION OF LIFESAVING TREATMENT FOR SEVERE MALARIA IN THE WARFIGHTER

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ABSTRACT

Quinidine is the only United States Food and Drug Administration (FDA) approved drug for the treatment of severe malaria. While it is commercially available and effective against malaria, it is not an ideal drug. Quinidine is associated with sudden cardiac death, principally via cardiac arrhythmias, and, because of its short half-life, must be administered 2-3 times a day. Most significantly, quinidine is no longer the drug of choice in treating certain electrocardiac disturbances and may soon cease to be available in the U.S.

Artemisinins are antimalarials derived from the Chinese herb, *Artemisia annua*. These compounds clear the parasites from the blood more rapidly than other antimalarial agents. Intravenous formulations of artemisinins have been used in much of the world and represent an improvement in efficacy and safety for severe malaria. There are currently no FDA-approved intravenous artemisinin products available in the U.S.

The Walter Reed Army Institute of Research has a long history with the artemisinins which has culminated in an intravenous artemisinin product. Between 2000 and 2002, two derivatives were in consideration (artesunate and artelinate) for development to licensure. After intense scrutiny and eventual consideration in committee at the Division of Experimental Therapeutics, artesunate was selected as the compound to put forward into advanced development. Artesunate is currently in use in much of the malarial world as a non- International Conference on Harmonisation (ICH) current Good Manufacturing Practices (cGMP) intravenous formulation produced in China and therefore gives us a potential wealth of clinical data. We envision our formulation of an ICH compliant, cGMP-produced, and FDA-licensed intravenous artesunate being available for use in the very near future for US military and civilians as well as eventual use worldwide. We have successfully filed an Investigational New Drug Application for this product and clinical trials with this agent are well underway. Our presentation will update the progress that has been made in preclinical studies, data from early current Good Clinical Practices (cGCP) Phase 1 trials (the first regulated Phase 1 work ever done with artesunate), data from early cGCP Phase 2 trials in Kenya, future planned clinical work, and our overall strategy for gaining full licensure of this product in the United States by the end of 2007.

1.0 INTRODUCTION

Worldwide, there are an estimated 200-300 million malaria cases a year, and at least 1-1.5 million deaths annually. Malaria patients unable to swallow antimalarial tablets, have evidence of vital organ dysfunction, or have a high parasite count are at risk of dying. Mortality due to *Plasmodium falciparum* malaria occurs primarily in persons without the immunity that results from previous infections. In heavily endemic areas such as sub-Saharan Africa, relatively nonimmune populations tend to be young children, or primigravida and secundigravida pregnant women whose placentas appear to have a particular affinity for *P. falciparum*. In less endemic areas, the whole population may not have effective immunity, and travelers to, especially military operating in, endemic regions are usually not immune.

Manifestations of a severe malaria infection can include cerebral, renal, pulmonary, and/or gastrointestinal pathology as the parasitized red blood cells become sticky and clump, blocking capillaries and causing organ dysfunction. In adults in endemic regions, the most common presentation of severe malaria is cerebral disease, including convulsions, focal neurologic signs, or coma, often complicated by retinal hemorrhage. Acute renal failure and acute pulmonary edema are frequent causes of mortality. In children in endemic regions, cerebral malaria is common, as are severe anemia, hypoglycemia with lactic acidosis, and/or respiratory impairment, any of which can cause mortality. Infection of pregnant women contributes to fetal distress and loss, and maternal anemia.

1.1 Treatment Options for Severe Malaria

Severe malaria is initially treated parenterally to rapidly lower the level of parasitemia to a non life-threatening level. A rapid decrease in peripheral parasitemia will also lead to reversal of any concomitant organ dysfunction. However, since end organ damage may have already occurred and quinoline "schizonticides" do not kill early schizonts in sequestered erythrocytes, a rapid decrease in peripheral parasitemia may not translate into complete reversal of organ damage. Comparative studies of parenteral antimalarials, in which patients were subsequently administered the same oral antimalarial irrespective of the parenteral agent initially used, the

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major endpoints of death, coma recovery time, permanent neurologic sequelae, and parasite clearance time were strongly influenced by the efficacy of the initial parenteral therapy.

When the parasitemia level has dropped to where a patient is able to tolerate oral medications, parenteral therapy is stopped and oral antimalarials are given to kill any remaining parasites. Oral antimalarials typically used include quinine, mefloquine, sulphadoxine-pyrimethamine, or, more recently, oral artemisinins.

Parenteral agents available for the worldwide treatment of severe malaria are primarily quinine (intramuscular or intravenous) or quinidine (intravenous). Despite appropriate medical care and prior parenteral quinine treatment, mortality from severe malaria remains approximately 20%.

1.1.1 Quinidine

Quinidine is the D-isomer of quinine, and is a more potent, but more toxic, antimalarial (White et al., 1983). Quinidine, which was also widely used as a Type I antiarrhythmic agent at the time, became the only parenteral antimalarial drug in the U.S. in 1991 due its ready availability. Quinidine is difficult to use due to its narrow therapeutic margin. It is given in slow infusions over 4 hours three times daily, and induces hyperinsulinemic hypoglycemia and causes significant cardiotoxicity requiring cardiac monitoring, if available. Furthermore, as cardiac uses of the drug have fallen due to the development of safer cardiac drugs, the potential market for quinidine has diminished, resulting in its limited availability in the United States. It is possible the manufacturer may discontinue its production due to the extremely small market.

1.1.2 Artemisinins

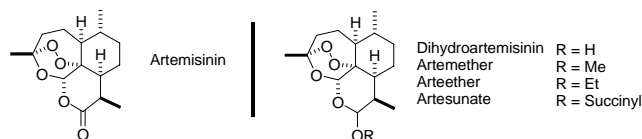


Figure 1. Chemical structure of the Artemisinins

Artemisinin, extracted from ‘qinghao’ or sweet wormwood (*Artemisia annua* L.) which has been part of traditional Chinese herbal medicine for centuries, was rediscovered and isolated in 1972 by Chinese scientists seeking new treatments for malaria, and was first reported in the medical literature in 1979 (QACG, 1979). The structure of artemisinin was determined to be a sesquiterpene lactone with an internal peroxide linkage. The biochemical mechanism of antimalarial action of the

artemisinins has been hypothesized to involve an iron-mediated cleavage of the endoperoxide bridge, producing oxygen radicals. Oxygen radicals can then react with nearby molecules. In support of this hypothesis, alkylation and polymerization of proteins and heme by artemisinin has been reported (Meshnick et al., 1993)

The various artemisinins in clinical use differ according to substituents at position C-10. Dihydroartemisinin (DHA; recently named arteminol; and referred to as dihydroquinhaosu (DQHS) in the older medical literature) is the most active compound in the class used clinically. Dihydroartemisinin is poorly water-soluble and is only available in a tablet formulation for oral use. Artemether (AM) and arteether/artemotil (AE), the methyl and ethyl ethers of dihydroartemisinin, respectively, are available in sesame oil for intramuscular injection.

1.1.2.1 Artesunate: Alternate Formulations for Treatment of Severe Malaria

“Artesunate for Injection,” a nonGMP parenteral (intravenous or intramuscular) formulation, has been developed and marketed by Guilin Pharmaceutical Company, Ltd. (Guangxi, China) and has been used clinically in Southeast Asia for a number of years. Given intravenously, it has been reported to be highly effective, and has the advantage of a consistent pharmacokinetic profile. In small studies, “Artesunate for Injection” appears to have a mortality benefit over intravenous quinine (Newton et al., 2000; Newton et al., 2003).

The Guilin IV Artesunate (AS) product was the subject of a recent multi-center, open-label randomized clinical trial designed to assess for a mortality benefit compared to IV quinine (Dondorp et al., 2005). This study was called the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT). Persons (age >2) with severe malaria based on clinical presentation and a positive HRP-2 (a *Plasmodium falciparum* antigen) rapid diagnostic test were eligible; significant pretreatment with quinine or artemisinin derivatives was exclusionary. Subjects were randomized to either standard dose IV quinine (20mg/kg load over 4 hours, then 10mg/kg q8 hours) or IV AS 2.4 mg/kg on admission, and again at 12h, and daily. Once able to take oral therapy, the volunteers completed a 7-day total course with oral quinine or AS, respectively. Doxycycline was added as part of the oral therapy (of either regimen) at some sites as recommended by national treatment guidelines. Primary study outcomes were death or survival to discharge from the hospital. There was no longer term follow-up. Secondary outcomes were the incidence of neurologic sequelae, neurologic recovery times (to eat,

speak and sit), time to hospital discharge and any new severe malaria complications.

1461 persons were enrolled and randomized, of which 1050 met severe malaria criteria once the full evaluation was completed. Among the 730 receiving IV AS, 633 were adults (75% male, 25% female) and 97 were children. 23 (17%) of the women were pregnant. The AS and quinine groups were comparable by a variety of severe malaria parameters. The trial was terminated at an interim analysis due to the statistically significant reduction in mortality in the AS arm.

Most of the mortality reduction benefit was seen in those who survived at least 48 hours, suggesting that early deaths were likely the result of organ failure not fully reversible by the parasite clearance. Mortality varied significantly between trial sites in different countries (low of 9% in Indonesia to 28% in Bangladesh) likely based on differences in adjunctive care available, but the relative benefit of AS was seen within all countries. There was no benefit in time to resolution of neurologic impairment or time to hospital discharge. A significantly higher percentage of hypoglycemia was seen in the quinine group, a known side effect of that drug. In subgroup analysis, hyperparasitemic ($>10\%$ parasitized RBCs) patients showed the greatest benefit from AS, likely due to its more rapid parasite clearance. However, all subgroups of severe malaria showed a trend towards better survival, and specific subgroups showing statistical mortality benefit included those patients with any anti-malarial pretreatment, those meeting the strict WHO definition of severe malaria, as well as those with jaundice or renal failure or acidosis or shock.

A meta-analysis of all randomized AS-quinine comparative studies ($n=1798$) using mortality as an endpoint showed a profound mortality reduction from AS ($p=0.00005$) as compared to standard doses of IV quinine.

In SEAQUAMAT, IV AS was again well tolerated. There was statistically ($p=0.009$) significant reduction in hypoglycemia post study entry, which is a known side effect of quinine and quinidine. There were no differences in the incidence of hemodynamic shock, convulsions, dialysis or mechanical ventilation. There was a higher non-statistical rate of hemoglobinuria and neurologic sequelae in the AS group among survivors, which may reflect the survival of severe cerebral cases who may have died in the quinine group. No other significant adverse events were attributed to AS.

Artesunate/bicarbonate buffer (Artesunate for Injection, Guilin) administered intravenously effectively

clears parasites at or above 1 mg/kg administered daily or twice on the first day. Regimens using 2.4 mg/kg clear parasites and resolve fever more quickly than IV quinine with fewer side effects. Comparative studies to parenteral quinine demonstrated statistically significant reductions in parasite clearance times, yet most studies have not shown significant differences in coma resolution times. The IV AS regimen of 2.4 mg/kg at entry followed by 1.2-2.4 mg/kg at 12 hours then 2.4 mg/kg daily is additionally associated with a mortality benefit in severe malaria in adults, and less side effects than IV quinine. Clinical side effects in these efficacy trials have been rare, but include rash (hives or a red rash), and possibly a higher incidence of blackwater fever. Minor side effects and laboratory abnormalities are often impossible to distinguish from the panoply of pathophysiologic effects of severe malaria.

2. CLINICAL DEVELOPMENT PLAN

The Walter Reed Army Institute of Research (WRAIR) has been working on the development of this product since a decision was made in 2000 to replace the current therapy for severe malaria. After two years of developing two different candidate artesiminins, a decision was made to develop AS as the final product and a concerted effort was put forward to get the Investigational New Drug application filed in late 2004. Figure 2 shows the current clinical development plan through licensure.

2.1 Phase 1 Safety Trials with Artesunate

WRAIR has completed one very intensive double blind, placebo controlled Phase 1 safety trial (labeled as the Phase 1a in Figure 2) with this drug in which volunteers received a single dose of the drug and were closely monitored for clinical, laboratory, and cardiovascular side effects from the drug. This was the first Good Clinical Practices trial ever done with intravenous AS. The Chinese had done a trial published in 1990 which concluded the drug was very safe in doses up to 16.88 mg/kg (Guo XB, et al. 1990). The doses in our trial ranged from 0.5 mg/kg, and then doubled to 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg and then finally 8 mg/kg. There were 6 active drug volunteers per group and two placebo volunteers. The drug was remarkably safe in this trial and there were very few adverse events noted in our work (see table 1). The only laboratory parameter that showed any change was reticulocytes that decreased and then rebounded exactly as in the Chinese trial without any adverse effects on the hematocrit (see figure 3).

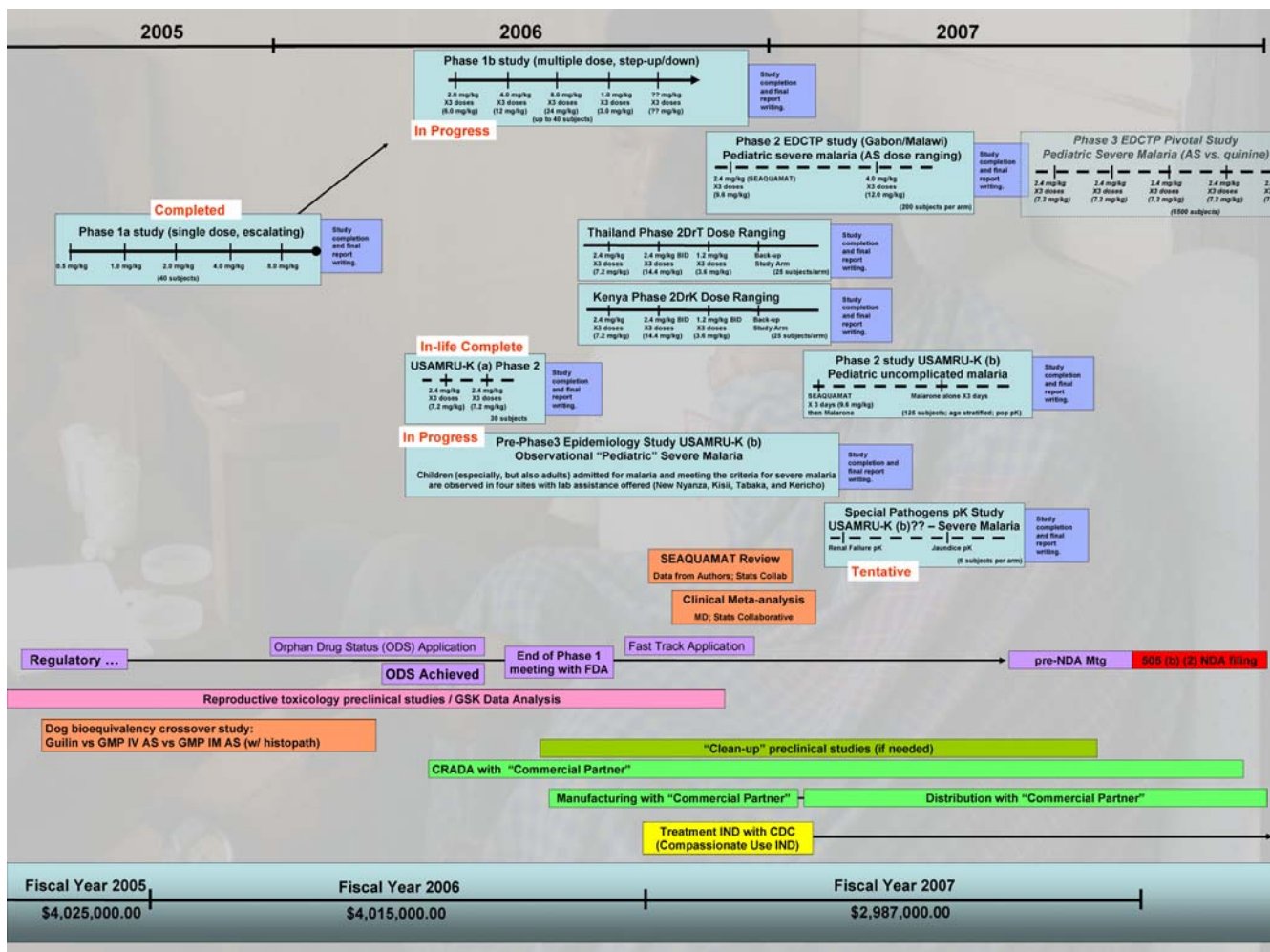


Figure 2. WRAIR's clinical development plan for Intravenous Artesunate through FDA licensure.

Table 1. Phase 1a Trial Adverse Events

<p>Most common Adverse Event (AE):</p> <p>Chemical Taste</p> <p>0 of 6* AEs in each of the ≤ 2.0 mg/kg cohorts</p> <p>5 of 6* AEs in the 4.0 mg/kg cohort</p> <p>5 of 6* AEs in the 8.0 mg/kg cohort</p> <p>All were graded as "mild" in severity</p> <p>All resolved quickly without interventions</p>
<p>Second most common Adverse Event (AE):</p> <p>Dizziness / Lightheadedness</p> <p>1 of 10 AEs in the placebo group</p> <p>1 of 6* AEs in the 2.0 mg/kg cohort</p> <p>2 of 6* AEs in the 4.0 mg/kg cohort</p> <p>3 of 6* AEs in the 8.0 mg/kg cohort</p> <p>All were graded as "mild" in severity</p>
<p>* There were 1 of 6 subjects in each of the 2.0, the 4.0, and the 8.0 mg/kg cohorts with no AEs</p>

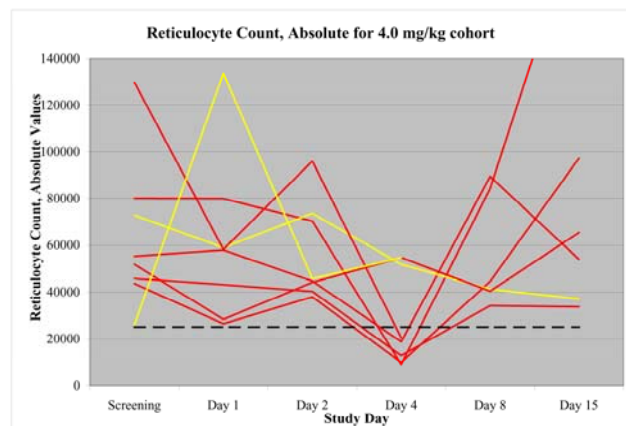


Figure 3. Reticulocytopenia followed by reticulocytosis after a single dose of IV AS at 4.0 mg/kg

This decrease in reticulocytes is most likely related to a temporary arrest of the basophilic erythroblast stage of the developing red blood cells which results in a brief “hole” in the release of reticulocytes from the bone marrow followed by a robust rebound of the “backed up” developing red cells. Further studies to elucidate this mechanism are needed to understand this phenomenon more fully, but this could be used as a reliable early marker for impending toxicity with the drug.

The second very intensive double blind, placebo controlled Phase 1 safety trial (labeled as the Phase 1b in Figure 2) with this drug is a modification of the first study. Volunteers receive multiple doses of the drug (3 are planned) and are closely monitored for clinical, laboratory, and cardiovascular side effects from the drug. The trial is ongoing as of the writing of this manuscript, but thus far, there have been no surprises and the adverse events and laboratory parameters have been the same as the first single dose safety trial.

2.2 Phase 2 Efficacy Trials

2.2.1 Prior Work with IV Artesunate

The primary producer of IV AS has been Guilin Pharmaceutical Company, Ltd., (Guangxi Province, China), who manufactures the drug in 60mg vials (under the brand name “Artesunate for Injection”) to be mixed in a two-step process: first the AS powder is dissolved with a 1mL ampoule of sodium bicarbonate buffer and then diluted with 5mL of intravenous solution, rendering a final concentration of 10 mg/mL. This product is sold in many other countries, often re-packaged by local distributors. All published studies to date have used this product.

Several small phase II trials of intravenous AS in uncomplicated falciparum malaria were completed by staff at the Guangzhou College of Traditional Chinese Medicine in the mid-1980s and have been summarized in English. The studies used a preliminary formulation (the quality was not defined) at a working concentration of 20 mg/mL, and the study methods, parasitological and safety assessments were also poorly defined. Limited dose ranging in persons with uncomplicated *P. falciparum* malaria administered low doses of IV AS once daily (0.25 mg/kg to 2 mg/kg at 0h, 4 h, 24h and 48 h) showed an initial plateau in parasite clearance above 1 mg/kg (Guo et al., 1990). Higher doses now in clinical use were not tested, and the dose ranging did not address the pharmacodynamic benefits of the second dose on the first day of therapy. In confirmatory studies in uncomplicated *P. falciparum* malaria, initial parasite clearance followed by high recrudescence rates (~50%) were reported after a

3-day course of IV AS (1.2 mg/kg at 0h, 4h, 24h and 48h), which could be substantially reduced using a 7-day regimen (Guo et al., 1990). In a randomized comparative trial for the treatment of uncomplicated *P. falciparum* (Li et al., 1990), 3 days of IV AS was compared to standard dose IV quinine for 3 days. Parasite clearance time was 20 hours faster in the AS group ($p=0.01$), and the fever clearance time was 12 hours faster ($p=0.01$). Recrudescence occurred in 50% of those treated with quinine and 56% of those treated with AS. Similar recrudescence rates have been observed in many studies with oral AS, and consequently the drug is routinely given with a second anti-malarial sequentially or concurrently for cure.

In severe malaria, a descriptive study by Guo et al (Guo et al., 1990) in 33 persons with cerebral malaria treated with 1-1.5mg/kg of IV AS for 3 days revealed survival in 94%, an improvement over that historically seen with quinine, and no attributable side effects of the AS were described. In non-randomized studies at the Hospital of Tropical Diseases in Bangkok, similar efficacy was seen when the doses in the first 12 hours were spaced 12 hours apart with notable improvement in parasite clearance times compared to historical IV quinine data (Krudsood et al., 2003). Several small open-label comparative randomized trials (Win et al., 1992; Vinh et al., 1997; Newton et al., 2003) have confirmed statistically improved parasitologic clearance of the Guilin IV AS compared to IV quinine. The sample sizes were not large enough to show a statistical mortality benefit, although mortality was uniformly lower in the AS treated groups. Coma recovery times were similar to IV quinine. Dosing regimens varied from 2-2.4 mg/kg initially, often with a second smaller dose (1.2 mg/kg) given at 12 hours and on subsequent days until a sequential oral therapy could be given.

2.2.2 WRAIR Trials with IV Artesunate

WRAIR has currently completed one trial of the efficacy of this drug in a Kenya (the USAMRU-Kenya (a) Phase 2 in figure 2). This trial had 30 subjects with a broad range of parasitemias upon entry into the trial. While the pharmacokinetic parameters have not been analyzed as of the writing of this manuscript, a preliminary analysis of the efficacy of the drug was able to be performed. Several important points are able to be appreciated from this work in Kenya. First, the parasite count continues to increase significantly, especially at the higher screening values (illustrated in figure 4). This is important because it points out that speed of therapy is crucial in malaria, especially in the non-immune population (the U.S. military).

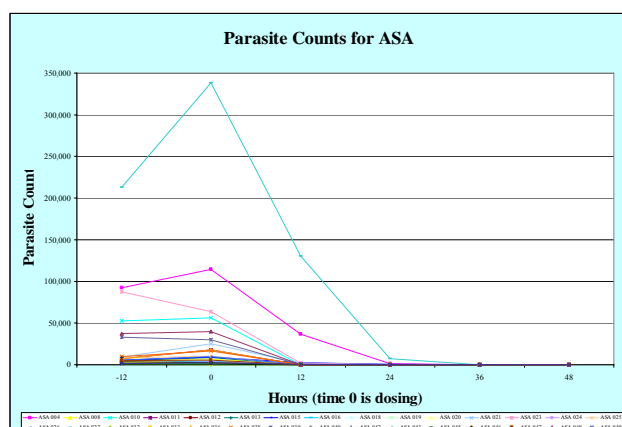


Figure 4. Parasite count changes before and after dosing with IV Artesunate in the Phase 2 trial in Kenya

Figure 4 also points out the rapidity of the action of this product in removing the parasite from the blood stream. If one normalizes the data (figure 5), the efficacy of this drug in treating malaria is quite evident. This data mirrors similar data with oral AS in published studies and the Guilin IV AS; both may allow use of prior published clinical trials in our filing and thereby accelerating our approval of this drug.

Figure 5 also suggests that there is both a parasite burden-dependent and parasite burden-independent delayed clearance. The parasite burden dependent clearance is not likely related to parasite factors (although resistance or a stage specific factor cannot be ruled out). It more likely reflects a pharmacokinetic issue such as slow drug delivery to some infected erythrocytes or host issues such as overwhelming splenic clearance mechanisms. The host burden-independent clearance may be explained by relatively resistant parasites or stage-dependent refractory parasites.

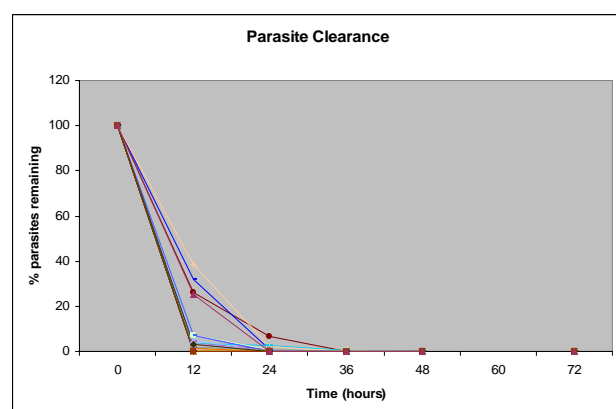


Figure 5. Parasite clearance with parasite numbers normalized to 100% of starting parasitemia in the Phase 2 trial in Kenya

We currently have several other Phase 2 clinical trials planned. The most important from our perspective is the dose ranging studies planned in Thailand and Kenya (seen as the 2DrT and 2DRK, respectively, in figure 2). While these studies are just getting underway as of the writing of this manuscript, we anticipate their completion in early 2007. These studies are important to provide additional safety data for the FDA licensure of this drug as well as to answer the important question posed by the SEAQUAMAT trial in which two doses were administered in the first 24 hours, followed by once daily dosing thereafter. Given the kinetics seen in parasite clearance illustrated in figure 5, one wonders if this is necessary and the potential risk of additional toxicity is justified in the therapy with this drug.

3.0 REGULATORY STRATEGY

The goal of the IV AS Integrated Product Team (IPT) is the rapid licensure of this drug to replace quinidine in the treatment of severe malaria. This is a more difficult task than often appreciated. It is widely appreciated how safe and effective this drug is in its extensive use throughout the world to date, but the currently used is neither current Good Manufacturing Practices produced nor FDA approved and therefore cannot be used by the U.S. military (or anywhere in the U.S. for that matter). Therefore, the principal goal is licensure, but the preferred goal is licensure in the most expeditious and direct manner while still assuring the safety and the quality of the product.

Following a traditional developmental path, this goal would be 4 years or more away at a minimum as a large and clearly expensive Phase 3 pivotal clinical trial would be required before licensure. This would significantly influence follow on products in the WRAIR drug pipeline as well as drain resources from other badly needed programs and projects within the WRAIR if the traditional path is not absolutely necessary. Because of this and the demonstrated safety and extensive testing the product has undergone, the IV AS IPT has chosen to attempt what is sometimes called a "paper Phase 3". The Chinese Guilin product was used in several trials, and most importantly in the pivotal SEAQUAMAT trial. Referencing this trial in our filing would allow more rapid approval of the drug for licensure.

By utilizing the similarities between the two products, we could remove several years and millions of dollars from the development plan for this product. For this plan to work, the team needed to get an idea of the FDA's views on this issue and recently had a very productive meeting with the Agency in which we received very positive responses to the following questions:

1) Does the Agency agree that the WRAIR IV AS and the Guilin IV AS are chemically equivalent based on data provided in the IND application and any supplemental submissions?

2) If the two products are deemed chemically equivalent, FDA regulations (21 CFR Part 320.22) state that bioequivalence studies are not required. The two products have different diluents though, so we do have limited bioequivalence data to report. We do not feel additional bioequivalence data is required (specifically, performance of the previously planned Phase 1c cross-over in Thailand with the two products). Does the Agency concur?

3) If the Agency believes the two products are chemically equivalent and bioequivalent, is cross-referencing clinical trials (such as SEAQUAMAT that use the Guilin formulation) appropriate in the WRAIR NDA filing?

4) We feel that an NDA filing using existing efficacy data [a literature-based 505(b)(2) filing] is acceptable to support the clinical indication of treatment of severe and complicated *falciparum* malaria in adults in the United States. Does the Agency concur?

5) We feel that given the lifesaving nature of this product, the existing neurotoxicity, cardiotoxicity, and reproductive toxicity studies already completed or in progress are adequate to support the desired indication. Does the Agency concur?

Virtually all of these questions were met with a positive response and most hinged on the first question regarding chemical equivalency of the two products. This question was answered by a comparison of the two different products in various potential diluents.

Table 2. Percentages SRI (Knoll) And Guilin AS Remaining In Solutions Of Phosphate And Of Bicarbonate/Glucose.

	Sample		Time	(Hr)	
			0	0.3	0.6
					0.9
SRI AS in 300mM Phosphate		100	99.36	98.96	98.77
Guilin AS in 300mM Phosphate		100	99.17	99.17	98.73
SRI AS in 1.0 mL Bicarbonate/Glucose		100	99.71	99.05	99.14
Guilin AS in 1.0 mL Bicarbonate/Glucose		100	99.92	99.45	99.31
SRI AS in 0.6 mL Bicarbonate/Glucose		100	99.53	99.31	98.93
Guilin AS in 0.6 mL Bicarbonate/Glucose		100	99.84	99.01	99.05

The above results clearly indicate that when dissolved in the same medium, solutions of SRI and Guilin AS show identical stability behavior (within experimental error).

Results in these tables show that after ≈ 3 hrs at room temperature, both SRI and Guilin AS solutions retain 96 to 97% of the time zero AS %. Pseudo-first-order rate plots for the SRI and Guilin AS solutions in each medium appear in Figures 6-8.

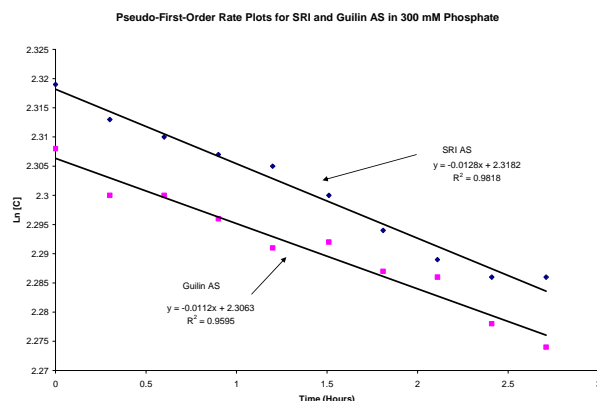


Figure 6. Pseudo-first-order rate plots for the SRI and Guilin AS dissolve in 300 mM phosphate to nominally 10 mg/mL

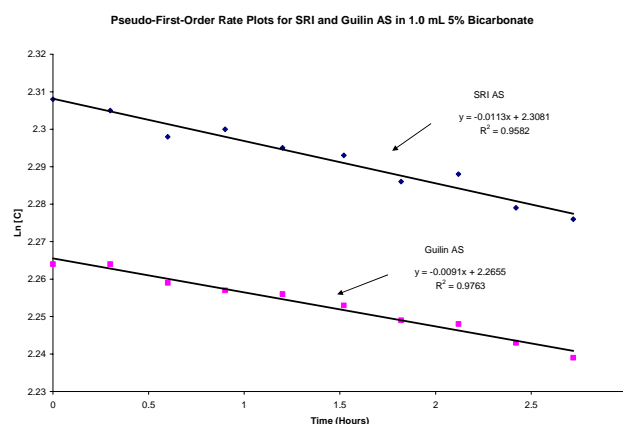


Figure 7. Pseudo-first-order rate plots for the SRI and Guilin AS in 1.0 mL bicarbonate, solution diluted with 5% glucose to nominally 10 mg/mL

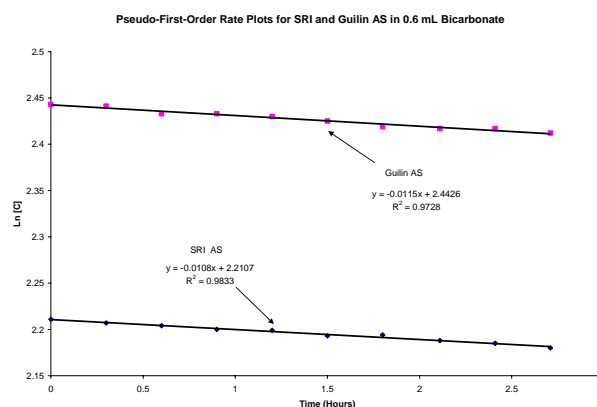


Figure 8. Pseudo-first-order rate plots for the SRI and Guilin AS in 0.6 mL bicarbonate, solutions with 5% glucose to nominally 10 mg/mL.

Summary

Artesunate is currently in use in much of the malarial world as a non- International Conference on Harmonisation (ICH) current Good Manufacturing Practices (cGMP) intravenous formulation produced in China. The licensure of an ICH, cGMP Intravenous Artesunate product in the United States would provide an important and vitally needed weapon in the fight against malaria in our military personnel and in U.S. travelers to malaria endemic parts of the world.

The Walter Reed Army Institute of Research has successfully produced such a product, has successfully filed an Investigational New Drug Application for this product, and final clinical trials with this agent are well underway. Data from early current Good Clinical Practices (cGCP) Phase 1 trials have shown this drug to be safe at doses well above that anticipated in clinical use, safe enough indeed to be used far forward of our current parenteral antimalarial product. Data from early cGCP Phase 2 trials in Kenya has demonstrated the efficacy and safety of this drug in malaria infected individuals and supports the published literature. Our strategy for gaining full licensure of this product in the United States by the end of 2007 / early 2008 has been validated by a recent meeting with the FDA. We envision our formulation of an ICH compliant, cGMP-produced, and FDA-licensed intravenous artesunate being available for use in the very near future for US military and civilians as well as eventual use worldwide.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

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